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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/874,992	06/12/1997	JONATHAN S. STAMLER	DUK97-02M	3513

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EXAMINER	
CELSA, BENNETT M	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 07/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/874,992	STAMLER, JONATHAN S.	
	Examiner	Art Unit	
	Bennett Celsa	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-17 and 59-71* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-17 and 59-71* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

Applicant's responses dated 4/21/04, is acknowledged.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Status of the Claims

Claims 15-17 and 59-71 are currently pending.

Outstanding Objection (s) and/or Rejection (s)

1. Claims 15, 17, 59-60 and 62-71 are rejected under 35 U.S.C. 102(e,f) as being anticipated, or alternatively under 35 USC 103 as being obvious over Stamler et al. US Pat. No. 6,471,978 (10/02: filed 6/2/95 or earlier).

Stamler et al. teach that nitric oxide (NO adducts) (e.g upon administration) and S-nitrosothiols (e.g. upon administration or formed in vivo upon NO adduct administration) cause vasodilation and platelet inhibition (e.g. see col 1) which prevents thrombus formation (e.g. see col. 2). Accordingly, the reference teaches that an administered "nitric oxide adduct" (e.g. a compound or a device comprising a compound: see col. 4) treats damaged vasculature which are susceptible to thrombus formation (e.g see col. 3). The selection of "nitric oxide adducts" of hemoglobin (e.g. (S) nitrosated/nitrated/polynitrosated) is anticipated or in the alternative obvious since hemoglobin is a preferred (e.g. claimed embodiment) "nitric oxide adduct" ie. includes nitrosohemeproteins, with hemoglobin being preferred. Eg. See patent claims 1, 18-24; 30, 36-42,48, and 54-60); *In re Schaumann*, 572 F.2d 312. 197 USPQ 5 (CCPA 1978)

Accordingly, the reference teaches treating (humans/animals) disorders resulting from platelet activation or adherence within the scope of the presently claimed invention (e.g. damaged vasculature) which inherently preventing thrombus formation and platelet activation. E.g. The prior art procedure inherently must prevent thrombus formation and platelet activation because the same protein is applied in the same way in the same amount. *In re Best*, 195 USPQ 430,433 (CCPA 1977); *Ex parte Novitski*, 26 USPQ2d 1389 (B.P.A.I, 1993).. Alternatively, the reference teaching of the use of NO adducts and S-nitrosothiols to inhibit platelet inhibit and prevent thrombus formation, where the selection of (S) nitrated/nitrosylated is anticipated or alternatively obvious (e.g. see patent claims), represents an explicit reference teaching anticipation or alternatively rendering obvious the use of these hemoglobins to prevent thrombus formation and platelet activation

Discussion

Applicant's arguments directed to the above 102/103 rejection were considered but deemed nonpersuasive for the following reasons.

Applicant alleges that 6,471,978 (col. 19, lines 6-19)describes methods of producing S-nitroso proteins which are not enabling to one of ordinary skill in the art to produce S-nitroso proteins or any other form of nitrosated/nitrated hemoglobins based on these methods since no information on the stability and/or biological activity of any hemoglobin derivative is given, or on its suitability as a coating for a medical device.

Applicant's argument was considered but not found persuasive for several reasons.

Initially, it is noted that neither applicant's claims, nor the '978 patent reference teachings are limited to S-nitrosylation but encompass the nitrosylation of additional nucleophilic protein (e.g. hemoglobin) groups. In this regard, the patent discloses (e.g. see col. 19-20 and examples) several different protocols for the (mono/poly) nitrosation/nitration of nucleophilic protein groups (e.g. thiol or otherwise), including hemoglobin. Applicant has neither provided sufficient facts nor other evidence to challenge the reference teaching nor the presumed validity afforded US Pat. No. 6,471,978.

Accordingly, the above rejection is hereby maintained.

2. Claims 15-17 and 59, 64-71 are rejected under 35 U.S.C. 102(e,f) as being anticipated, or alternatively under 35 USC 103 as being obvious over Stamler et al. US Pat. No. 6,583,113 (06/03: filed 3/24/95 or earlier).

Stamler et al. teach that nitric oxide (NO adducts) (e.g upon administration) and S-nitrosothiols (e.g. upon administration or formed in vivo upon NO adduct administration) cause vasodilation and platelet inhibition (e.g. see col 1; examples, particularly Ex. 7) which prevents thrombus formation (e.g. see columns. 2 and 4) for treating/preventing cardiovascular disorders (e.g. "A disorder resulting from platelet activation or adherence"). including cardiac failure and myocardial infarction (e.g. see col. 4, claims 1-4). The selection of hemoglobin (e.g. (S) nitrosated/nitrated/polynitrosated) is anticipated or in the alternative obvious since hemoglobin is preferred (e.g. examples; claimed embodiment) Eg. See patent claims 1-4 and *In re Schaumann*, 572 F.2d 312. 197 USPQ 5 (CCPA 1978) . Accordingly, the

reference teaches treating (humans/animals) disorders resulting from platelet activation or adherence within the scope of the presently claimed invention (e.g. cardiovascular disorders or clotting disorders) which inherently prevent thrombus formation and platelet activation. E.g. The prior art procedure inherently must prevent thrombus formation and platelet activation because the same protein is applied in the same way in the same amount. *In re Best*, 195 USPQ 430,433 (CCPA 1977); *Ex parte Novitski*, 26 USPQ2d 1389 (B.P.A.I, 1993). Alternatively, the reference teaching of the use of NO adducts and S-nitrosothiols to inhibit platelet inhibit and prevent thrombus formation, where the selection of (S) nitrated/nitrosylated hemoglobin is anticipated or alternatively obvious (e.g. see patent claims), represents an explicit reference teaching anticipation or alternatively rendering obvious the use of these hemoglobins to prevent thrombus formation and platelet activation

Discussion

Applicant's arguments directed to the above 102/103 rejection over the 6,583,113 patent were considered but deemed nonpersuasive for the following reasons. Initially, it is noted that the above rejection was modified to remove claims 60-63 which is specifically directed to "nitrosylhemoglobin" thus rendering moot arguements directed thereto.

Applicant first notes that the Stamler '113 patent reference has the same content as WO 93/09806 with the exception of the claims and then argues that there is no evidence presented in US Patent No. 6,583,113 that any form of nitrosated or nitrated

hemoglobin has any biological activity that can be applied to any disease or medical condition.

This argument was considered but deemed nonpersuasive for the following reasons.

The rejection above clearly points out that Stamler et al '113 patent reference teaches that nitric oxide (NO adducts) (e.g upon administration) and S-nitrosothiols (e.g. upon administration or formed in vivo upon NO adduct administration) cause vasodilation and platelet inhibition (e.g. see col 1; examples, particularly Ex. 7) which prevents thrombus formation (e.g. see columns. 2 and 4) for treating/preventing cardiovascular disorders (e.g. "A disorder resulting from platelet activation or adherence") including cardiac failure and myocardial infarction (e.g. see col. 4, claims 1-4).

Applicant further alleges that "One of ordinary skill in the art would conclude from Example 19 of 6,583,113 that the syntheses of SNO-hemoglobin failed".

This argument is not found persuasive since applicant has not provided sufficient facts or other evidence to challenge the presumed validity afforded US Pat. No. 6,583,113.

Additionally, Applicant's argument is not persuasive since applicant's arguments are not commensurate in scope with the presently claimed invention which are not limited to nitrosylhemoglobin or SNO-hemoglobin, but encompass other species of nitrosylated heme containing NO donating compounds including (mono/poly) thiolated hemoglobins. In this respect, Applicant's argument fails to appreciate the patent

reference teaching as a whole in which the reference teaching of the therapeutic use of nitrosylated/nitrosated hemoglobin genus (e.g. in general) would include polynitrosated hemoglobins; e.g. the reference teaching of thiolating proteins (e.g. hemoglobin) /amino acids at positions other than at thiols (or metal), including oxygen, carbon and nitrogen for achieving regulation of protein/amino acid function; such derivatives being within the scope of the presently claimed broad "nitrosated hemoglobin" generic.

Applicant argues that the teachings of Stamler et al. (US Patent No. 6,583,113:Example 19) is equivalent to WO 93/09806; and that the WO 93 reference fails to teach a method of making S-nitrosylhemoglobin; nor is it enabling in view of the Stamler 132 Declaration mailed January 6, 1999 attacking Example 19 of WO 93. Initially it is noted that this argument is not persuasive since it's no commensurate to the presently claimed invention which is not so limited. The claims broadly address the use of mono/poly nitrosated/nitrated hemoglobins" which encompass Hb nitroslation/nitration at other sites other than thiols or metals. Accordingly, the Stamler references (WO 93 and 6,583,113) teach the use of nitrosylated hemoglobins which includes NO groups attached to "additional sites such as oxygen, carbon and nitrogen" (e.g. see '113 patent abstract; col. 1) and is not so limited to nitrosylhemoglobin or S-nitrosylhemoglobin.

Secondly, the claimed subject matter of US Pat. No. 6,583,113 is presumed valid e.g. enabled.

Further, with respect to S-nitrosylation of proteins including hemoglobin , Stamler WO93 and US Pat. 6,583,113 disclose different methods for thiol nitrosylation of

proteins not addressed by the Stamler Declaration (e.g. as disclosed on page 30-31 of the WO 93 document and col. 15-17 of '113 patent) which include:

1. reaction of nitrosylating agent (e.g. equimolar amounts of acidic NaNo2 as nitrosating agent in a buffered saline at pH 7.4 for tPA);

2. exposure of the protein (e.g. tPA to NO gas in buffered saline)

With regard to the above, Stamler WO 93further notes that other oxides of nitrogen can be utilized (e.g. NOCL, N2O3) as well as other nitroso equivalents. Optimization of reaction conditions, including pH, is within the skill of the art. Accordingly, the WO 93 and the issued patent reference clearly teaches synthesizing thionitrosylated hemoglobin by using optimized amounts (e.g. nitrosating agent, low molecular weight S-nitrosothiol), with further optimization of pH during nitrosylation to form a more stable nitrosylated oxy/deoxy hemoglobin.

Applicant alludes to a February 13th 2001 telephonic interview held with the Examiner, attorney Carol Egner and the inventor Jonathan Stamler referring to the Stamler 132 Declaration filed 6 January 1999 and accompanying exhibits to which it is asserted that "the Examiner stated that he accepted that WO 93/09806 does not present an enabling description of a method to produce S-nitrosohemoglobin."

Applicant's argument was considered but deemed nonpersuasive for the following reasons.

Both the "Interview Summary Record" in the parent application 08/796,164 (mailed 10/22/03) and the "Interview Summary Record" in the present 08/874,992 application (mailed February 26, 2001) indicate that "agreement was not reached" and

under the heading "Description of the general nature of what was agreed to if an agreement was reached, or any other comments" it is stated that "Applicant presented arguments to traverse the rejections of record and will consider the filing of further supplemental responses as deemed appropriate". Thus, a decision regarding the enablement of the WO 93/09806 reference was not made by the Examiner during the February 13, 2001 telephonic interview. A copy of the "Interview Summary Record" mailed February 26, 2001 is hereby enclosed.

Accordingly, the above rejection is hereby maintained.

Double Patenting

3. Claims 15, 17, 59 and 64-71 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-65 (especially claims 1, 2, 5,6, 18, 20-24; 30, 36-42, 48, and 54-60) of U.S. Patent No. 6,471,978 alone or in combination with its disclosure (e.g. abstract; col. 1-4) for purposes of demonstrating claim interpretation and/or inherency. Although the conflicting claims are not identical, they are not patentably distinct from each other because :

Stamler et al. teach (e.g. see patent claims 1, 30, 48,) that nitric oxide (NO adducts) and S-nitrosothiols, upon in vivo administration (e.g. local or systemic: see patent claims 5 and 6; i.e. to a "patient" who is a "human" or "animal" w/n the scope of the present claims: see '978 abstract) prevents/inhibits platelet deposition and "alleviates" (e.g. treats) restenosis (e.g. see col 1; patent claim 2) which serves to "inherently" prevent thrombus formation (e.g. see '978 col. 2).

Accordingly, the patented invention teaches the administration (e.g. local/systemic) of "nitric oxide adducts" to: a. inhibit platelet activation and b. prevent/inhibit/treat "a disorder resulting from platelet activation or adherence in an animal or human" (e.g. restenosis or damaged vasculature) within the scope of present claims Further, the selection of "nitric oxide adducts" of modified hemoglobin (e.g. (S) nitrosated/nitrated/polynitrosated) is anticipated or in the alternative obvious since hemoglobin is a preferred (e.g. claimed embodiment). Eg. See patent claims 1, 18-24; 30, 36-42,48, and 54-60). See *In re Schaumann*, 572 F.2d 312. 197 USPQ 5 (CCPA 1978). Accordingly, the reference teaches treating (humans/animals) disorders resulting from platelet activation or adherence within the scope of the presently claimed invention (e.g. damaged vasculature) which inherently preventing thrombus formation and platelet activation. E.g. The prior art procedure inherently must prevent thrombus formation and platelet activation because the same protein is applied in the same way in the same amount. *In re Best*, 195 USPQ 430,433 (CCPA 1977); *Ex parte Novitski*, 26 USPQ2d 1389 (B.P.A.I, 1993). Alternatively, the reference teaching of the use of NO adducts and S-nitrosothiols to inhibit platelet inhibit and prevent thrombus formation, where the selection of (S) nitrated/nitrosylated is anticipated or alternatively obvious (e.g. see patent claims), represents an explicit reference teaching anticipation or alternatively rendering obvious the use of these hemoglobins to prevent thrombus formation and platelet activation.

Discussion

Applicant's arguments were considered but deemed nonpersuasive for the following reasons. Initially, it is noted that the above rejection was modified to remove present claims addressing nitrosylhemoglobin which is not explicitly taught by the reference.

Applicant first argues that patent claims 1-65 require "a damaged vascular surface" not required by the present claims. Additionally, applicant further asserts that "[T]reating an animal or human disorder resulting from platelet activation or adherence is not within any of the embodiments of any of the claims of US 6,471,978".

These arguments were considered but deemed nonpersuasive. The above rejection details how the patent claims provide a teaching of administering (e.g. local/systemic etc.) nitrous oxide releasing compounds (e.g. nitrous oxide adducts) to inhibit platelet activation and treat "a disorder resulting from platelet activation or adherence in an animal or human "(e.g. restenosis or vessel damage) within the scope of the presently claimed invention.

Applicant argues that the "class of agents" in claims 1-65 of 6,471,978 is extremely broad and includes compounds with no demonstrated ability to release NO and therefore it is not true that "the same protein is applied in the same way in the same amount".

This argument was considered but deemed nonpersuasive. The above rejection clearly points out that several different sets of dependent patent claims carve out a "preferred" embodiment of nitrous oxide adducts (e.g. NO donating) compounds which encompass modified hemoglobin (e.g. (S) nitrosated/nitrated/polynitrosated) the selection of which is anticipated or rendered obvious by these dependent patent claims. Eg. See patent claims 1, 18-24; 30, 36-42,48, and 54-60).

Applicant argues that "[I]t is not apparent to one of ordinary skill in the art why agents that must be applied to a damaged vascular surface for the purpose of treating that damage vascular surface, and are not effective if administered systemically (see Figure 3 and column 28, line 58 to column 29, line 3) would have any effect on platelet aggregation in an animal or human."

This argument was considered but deemed nonpersuasive for the following reasons.

As discussed above, the patent claims provide a teaching of administering (e.g. *local/systemic* etc.) NO releasing compounds (e.g. nitrous oxide adducts) to inhibit platelet activation and treat "a disorder resulting from platelet activation or adherence in an animal or human "(e.g. restenosis or vessel damage) within the scope of the presently claimed invention. Figure 3 and column 28, line 58 to column 29, line 3 referred to by applicant merely disclose that iodine labelled S-NO-BSA administered locally and systemically to balloon-injured rabbit femoral artery binds more when administered locally as compared to systemically. It is noted, however, that systemic administration still shows greater binding as compared to a control. In this regard it is noted that the patent claims (and Figure 3) teach both local and systemic administration (e.g patent claims 5 and 6) which is within the scope of the presently claimed invention. Additionally, the example addresses S-NO-BSA and not the corresponding hemoglobin derivative; and in any event does achieve some degree of systemic binding

Applicant queries why the Examiner refers to the patent specification when the patent claims, for purposes of double patenting are at issue; and questions the applicability of *In re Schaumann* decision in the present context (e.g. double patenting rejection).

These arguments were considered but deemed nonpersuasive for the following reasons.

Initially, it is noted that courts have acknowledged that patent claims are not interpreted in a vacuum, and reference back to the patent's specification for *purposes of claim interpretation* (e.g. determine what is being claimed), even in the context of double patenting, is acceptable. E.g. *In re Higgins et al.* (CCPA 1966) 369 F2d 414, 152 USPQ 103. Additionally, in satisfying the Examiner's burden of demonstrating *inherency of a claim limitation* any source of "extrinsic evidence" is permissible [(e.g. citation of references or other evidence: See MPEP 2131.01(d); See *In re Best*, 195 USPQ 430,433 (CCPA 1977)(inherent anticipation regarding prevention);], as well as the use of "intrinsic" evidence, which include applicant's own specification . *See Ex parte Novitski*, 26 USPQ2d 1389 (B.P.A.I, 1993) (Board consulted applicant's own Experimental Results to demonstrate inherency of method preamble limitation). Accordingly, for purposes or demonstrating claim limitation inherency or claim interpretation, the use of "intrinsic evidence" (e.g. within the four corners of the specification) is entirely proper; even in the context of double patenting.

Applicant's argument fails to appreciate the patent claims (e.g. especially the dependent claims) teaching as a whole which anticipates or render obvious the selection of modified hemoglobins in a manner consistent with *In re Schaumann*, 572 F.2d 312. 197 USPQ 5 (CCPA 1978). With respect to anticipation and obviousness regarding a reference teaching of a limited genus or markush listing of compounds applicant is further referred to MPEP 2131.02

(anticipation) and MPEP 2144.08 (obviousness) both of which sections further discuss the *In re Schaumann* CCPA decision.

Additionally, the rejection above makes reference to the '978 specification for purposes of claim interpretation and inherency. For example, the patented claim method objectives include the following:

a. treat a damaged vascular surface in which damage to the endothelium or subendothelium, narowing or stenosis of the vessel has occured (e.g. see patent claim 1);

b. wherein the method for treating ... is a method of preventing or inhibiting platelet deposition or for alleviating restenosis (e.g. see patent claim 2); and

c. wherein the nitric oxide adduct delivers at least one of a nitrosium ion or a nitroxyl ion physiological conditions (e.g. see patent claims 13 and 49);

However, while the claims broadly encompass any means of "administering" NO HOST is recited in the claims. For purposes of claim interpretation (e.g. designing around/infringement etc.) **determination of the host (e.g. the recipient of the administering) is a question of claim interpretation** to which "intrinsic" evidence (e.g. the '978 specification) is at issue. From the patent claims it is clear that the host to be treated must have had a disease/disorder or other malady that:

a. resulted in "a damaged vascular surface" with "narrowing or stenosis of the vessel" (corresponding to item a. above) ;

b. result in or otherwise involves aberrant platelet deposition and/or restenosis (corresponding to item b above); and/or

c. is preventable or treatable by administering an NO (e.g. nitrosium ion or a nitroxyl ion) donating compound (e.g. corresponding to item c. above)

which include patients e.g "animal or human" within the scope of the present claims.

Accordingly, for all the reasons recited above, the double patenting rejection is hereby retained.

4. Claims 15-17 and 59 and 64-71 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 6,583,113 alone or in combination with its disclosure (e.g. col. 1-5; examples) for purposes of interpreting claim scope and/or demonstrating inherency. Although the conflicting claims are not identical, they are not patentably distinct from each other because :

Patent claim 1 teaches preventing or treating " a disease or disorder in a "patient in need thereof" comprising "delivering"nitric oxide to a targeted site in the body of a patient from a nitrosated and/or nitrosylated "heme protein", wherein the heme protein is nitrosated and/or nitrosylated at one or more thiol groups in the heme protein. See patent claim 1. Patent claims 2-4 specify that the "heme protein" is hemoglobin (e.g .human) and that the "disease or disorder" encompasses " (cardiovascular) disorder(s) resulting from platelet activation or adherence" such as myocardial infraction .

The term "delivery" to a "patient in need thereof" clearly encompasses administration of a pharmaceutical composition to a human or animal as presently claimed. For example, the '113 patent specification (e.g. col. 4) establishes that the claimed "delivery" of nitrosylated/nitrosated hemoglobin to a "patient" to "effect vasodilation, platelet inhibition and thrombolysis" (inherently) as well as treat "cardiovascular disorders" clearly encompass "administration" of

pharmaceutical compositions to patients which are "human" and/or "animal" within the scope of the presently claimed invention. See e.g. '113 col. 4-5 and examples.

Accordingly, Stamler et al. teach that nitric oxide (NO adducts) (e.g upon administration) and S-nitrosothiols (e.g. upon administration or formed in vivo upon NO adduct administration) cause vasodilation and platelet inhibition (e.g. see col 1; examples, particularly Ex. 7) which prevents thrombus formation (e.g. see columns. 2 and 4) for treating/preventing cardiovascular disorders (e.g. "A disorder resulting from platelet activation or adherence"). including cardiac failure and myocardial infarction (e.g. see col. 4, claims 1-4). The selection of hemoglobin (e.g. (S) nitrosated/nitrated/polynitrosated) is anticipated or in the alternative obvious since hemoglobin is preferred (e.g. examples; claimed embodiment) Eg. See patent claims 1-4 and *In re Schaumann*, 572 F.2d 312. 197 USPQ 5 (CCPA 1978) . Accordingly, the reference teaches treating (humans/animals) disorders resulting from platelet activation or adherence within the scope of the presently claimed invention (e.g. cardiovascular disorders or clotting disorders) which inherently prevent thrombus formation and platelet activation. E.g. The prior art procedure inherently must prevent thrombus formation and platelet activation because the same protein is applied in the same way in the same amount. *In re Best*, 195 USPQ 430,433 (CCPA 1977); *Ex parte Novitski*, 26 USPQ2d 1389 (B.P.A.I, 1993). Alternatively, the reference teaching of the use of NO adducts and S-nitrosothiols to inhibit platelet inhibit and prevent thrombus formation, where the selection of (S) nitrated/nitrosylated hemoglobin is anticipated or alternatively obvious (e.g. see patent claims), represents an explicit reference teaching anticipation or

alternatively rendering obvious the use of these hemoglobins to prevent thrombus formation and platelet activation.

Discussion

Applicant's arguments were considered but deemed nonpersuasive for the following reasons. Initially, it is noted that the above rejection was modified e.g. to remove claims 60-63 addressing nitrosylhemoglobin which is not explicitly taught by the reference.

Applicant argues that claims 1-4 of US 6,583,113 does not comprise a step of administering to a human a composition comprising a nitrosated/nitrosylated hemoglobin and additionally claims 1-4 read on a process that occurs naturally in nature (e.g. red blood cells).

Applicant's arguments were considered but deemed nonpersuasive for the following reasons.

Initially, whether the patent claims encompass "a process that occurs in nature" is not germaine as long as the patent claims encompass the presently claimed process steps. As pointed out in the above rejection, Patent claim 1 teaches preventing or treating " a disease or disorder in a "patient" in need thereof" comprising "delivering"nitric oxide to a targeted site in the body of a patient using a nitrosated and/or nitrosylated "heme protein", wherein the heme protein is nitrosated and/or nitrosylated at one or more thiol groups in the heme protein; wherein the term "delivery" to a "patient in need thereof" clearly encompasses administration of a pharmaceutical composition to a human or animal as presently claimed. See e.g. patent columns 4-5.

Applicant argues that the content of US 6,583,113 patent is the same as that of WO 93/09806, with the exception of the claims and Applicant alludes to a February 13th

2001 telephonic interview held with the Examiner, attorney Carol Egner and the inventor Jonathan Stamler referring to the Stamler 132 Declaration filed 6 January 1999 and accompanying exhibits to which it is asserted that "the Examiner stated that he accepted that WO 93/09806 does not present an enabling description of a method to produce S-nitrosohemoglobin."

Applicant's argument was considered but deemed nonpersuasive for the following reasons.

Both the "Interview Summary Record" in the parent application 08/796,164 (mailed 10/22/03) and the "Interview Summary Record" in the present 08/874,992 application (mailed February 26, 2001) indicate that "agreement was not reached" and under the heading "Description of the general nature of what was agreed to if an agreement was reached, or any other comments" it is stated that "Applicant presented arguments to traverse the rejections of record and will consider the filing of further supplemental responses as deemed appropriate". Thus, a decision regarding the enablement of the WO 93/09806 reference was not made by the Examiner during the February 13, 2001 telephonic interview. A copy of the "Interview Summary Record" mailed February 26, 2001 is hereby enclosed.

To the extent that applicant is arguing the nonenablement of US Pat. No. 6,583,113 patent, this argument was considered but deemed nonpersuasive for the following reasons.

Initially, it is noted that U.S. patent, 6,583,113.is presumptively valid (e.g. enabled).

In this respect, applicant argument is not persuasive since applicant's arguments are not commensurate to the scope of the presently claimed invention which are not limited to nitrosylhemoglobin, but encompass other species of nitrosylated heme containing NO donating compounds including thiolated hemoglobins. In this respect, Applicant's argument fails to appreciate the patent reference teaching as a whole in which the reference teaching of the therapeutic use of nitrosylated/nitrosated hemoglobin genus (e.g. in general) would include polynitrosatedhemoglobins; e.g. the reference teaching of thiolating proteins (e.g. hemoglobin) /amino acids at positions other than at thiols (or metal), including oxygen, carbon and nitrogen for achieving regulation of protein/amino acid function; such derivatives being within the scope of the presently claimed broad "nitrosated hemoglobin" generic.

Further, with respect to S-nitrosylation of proteins including hemoglobin , Stamler WO93 and US Pat. 6,583,113 disclose different methods for thiol nitrosylation of proteins not addressed by the Stamler Declaration (e.g. as disclosed on page 30-31 of the WO 93 document and col. 15-17 of '113 patent) which include:

1. reaction of nitrosylating agent (e.g. equimolar amounts of acidic NaNo2 as nitrosating agent in a buffered saline at pH 7.4 for tPA);

2. exposure of the protein (e.g. tPA to NO gas in buffered saline)

With regard to the above, Stamler WO 93further notes that other oxides of nitrogen can be utilized (e.g. NOCL, N2O3) as well as other nitroso equivalents.

Accordingly, applicant has not provided sufficient facts or other evidence to challenge the presumed validity afforded US Pat. No. 6,583,113.

Applicant further argues that the office erroneously failed to arrive at the correct inventorship result regarding a Rule 1.63 petition in the 09/092,622 application (now US 6,291,424) which is the parent of 09/835,038 (now US 6,583,113) which would have removed Dr. Stamler as an inventor of US 6,583,113; thus rendering double patenting inapplicable. .

This argument is not persuasive since the issued patent, presumed valid, lists Dr. Stamler as an inventor.

Accordingly, the above rejection is hereby maintained.

5. Claims 15-17, 59 and 64-71 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-17 (especially claims 3-9 and 17) of copending Application No. 10/216,865 (PG Pub. US 2003/0007967) to Stamler et al. alone or in combination with its disclosure (e.g. col. 1-4; examples) for purposes of interpreting claim scope and/or demonstrating inherency.

The patent claims teach:

Pharmaceutical compositions including a (poly) nitrosyl/nitrosated hemoglobin/methemoglobin (e.g. S-nitroso-hemoglobin/myoglobin) for administration to an "animal" to:

a. inhibit platelet function (causing vasodilation or relaxing non-vascular smooth muscle) (e.g. patent claims 7 and 8); and/or

b. treat/prevent a "cardiovascular disorder" (e.g. patent claim 9); and

c. delivering nitric oxide to one or more specific target sites (e.g. patent claim 17)

Inhibition of platelet activation (e.g. present claims 59, 70 and 71) is clearly within the scope of the claimed patent inhibition of platelet function. See e.g. 10/216,865 page 12 (bottom left column to top right column) and Figure 8.

Treatment of "disorders resulting from platelet activation" (e.g. myocardial infarction ;see present claims 15-16, 64,66, 67) is clearly within the scope of the claimed treatment/prevention of a "cardiovascular disorder" (e.g. see 10/216,865 page 7).

The claims treatment of "animals" would immediately envisage or alternative render obvious the use of the claimed pharmaceutical compositions in "humans" (e.g. see also bottom right column on page 7 to page 8 referring to "patients" , "individuals" i.e. utilization of terminology attributed to humans). See *In re Schaumann*, 572 F.2d 312. 197 USPQ 5 (CCPA 1978).

The presently claimed "prevention of thrombus formation" (e.g. present claims 17, 68, and 69) and "inhibiting platelet activation" inherently must occur by practice of the patented methods as supported by the patent application disclosure (e.g. 10/216,865 example6: anti-thrombotic) and established case law . E.g. The prior art procedure inherently must prevent thrombus formation and platelet activation because the same protein is applied in the same way in the same amount. *In re Best*, 195 USPQ 430,433 (CCPA 1977); *Ex parte Novitski*, 26 USPQ2d 1389 (B.P.A.I, 1993).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Discussion

Applicant's arguments directed to the above provisional double patenting rejection were considered but deemed nonpersuasive for the following reasons. Initially,

it is noted that the above rejection was modified to remove claims 60-63 which is specifically directed to "nitrosylhemoglobin" thus rendering moot arguements directed thereto.

Applicant argues that the claims of copending Application No. 10/216,865 do not render obvious the presently claimed invention and requests clarification as to how the description of this application is being applied to the present claims.

This argument was considered but deemend nonpersuasive for the following reasons.

The above modified rejection clearly points out how the claims, and where necessary the patent application specification (and how the specification is applied to interpret the claims and demonstrate inherency) , render obvious the presently claimed invention. It is noted that courts have acknowledged that patent claims are not interpreted in a vacuum, and reference back to the patent's specification for *purposes of claim interpretation* (e.g. determine what is being claimed), even in the context of double patenting, is acceptable. E.g. *In re Higgins et al.* (CCPA 1966) 369 F2d 414, 152 USPQ 103. Additionally, in satisfying the Examiner's burden of demonstrating *inherency of a claim limitation* any source of "extrinsic evidence" is permissible [(e.g. citation of references or other evidence: See MPEP 2131.01(d); See *In re Best*, 195 USPQ 430,433 (CCPA 1977)(inherent anticipation regarding prevention);], as well as the use of "intrinsic" evidence, which include applicant's own specification . *See Ex parte Novitski*, 26 USPQ2d 1389 (B.P.A.I, 1993) (Board consulted applicant's own Experimental Results to demonstrate inherency of method preamble limitation). Accordingly, for purposes of demonstrating claim limitation inherency or claim interpretation, the use of "intrinsic evidence"

(e.g. within the four corners of the specification) is entirely proper; even in the context of double patenting.

Applicant further argues that the 10/216,865 application claims are not enabling as to the making and use of their hemoglobin compositions. In this regard, applicant argues that the content of 10/216,865 is the same as that of WO 93/09806, with the exception of the claims and applicant and argues that there is no evidence that "any amount of SNO-hemoglobin was ever produced" and alludes to a February 13th 2001 telephonic interview held with the Examiner, attorney Carol Egner and the inventor Jonathan Stamler on February 13, 2001 referring to the Stamler 132 Declaration filed 6 January 1999 and accompanying exhibits to which it is asserted that "the Examiner stated that he accepted that WO 93/09806 does not present an enabling description of a method to produce S-nitrosohemoglobin."

Applicant's argument was considered but deemed nonpersuasive for the following reasons.

Initially, it is noted that the 10/216,865 application provides ample enablement as to the therapeutic use of its compositions. E.g. pages 7-8 and Examples.

Regarding enablement of "making" it is noted that both the "Interview Summary Record" in the parent application 08/796,164 (mailed 10/22/03) and the "Interview Summary Record" in the present 08/874,992 application (mailed February 26, 2001) indicate that "agreement was not reached" and under the heading "Description of the general nature of what was agreed to if an agreement was reached, or any other comments" it is stated that "Applicant presented arguments to traverse the rejections of

record and will consider the filing of further supplemental responses as deemed appropriate". Thus, a decision regarding the enablement of the WO 93/09806 reference was not made by the Examiner during the February 13, 2001 telephonic interview. A copy of the "Interview Summary Record" mailed February 26, 2001 is hereby enclosed.

Further, with respect to S-nitrosylation of proteins including hemoglobin , Stamler WO93 and the 10/216,865 application both disclose different methods for thiol nitrosylation of proteins not addressed by the Stamler Declaration (e.g. as disclosed on page 30-31 of the WO 93 document) which include:

1. reaction of nitrosylating agent (e.g. equimolar amounts of acidic NaNo2 as nitrosating agent in a buffered saline at pH 7.4 for tPA);

2. exposure of the protein (e.g. tPA to NO gas in buffered saline)

With regard to the above, Stamler WO 93 further notes that other oxides of nitrogen can be utilized (e.g. NOCL, N2O3) as well as other nitroso equivalents.

Accordingly, the WO 93 and 10/216,865 application are enabling since applicant has not provided sufficient facts or other evidence to the contrary.

Applicant further argues that the office erroneously failed to arrive at the correct inventorship result regarding a Rule 1.63 petition in the 09/092,622 application (now US 6,291,424) which is the parent of 09/835,038 (now US 6,583,113) which would have removed Dr. Stamler as an inventor of US 6,583,113; thus rendering double patenting inapplicable. .

This argument is not persuasive since the issued patent, presumed valid, lists Dr. Stamler as an inventor.

Accordingly, the above rejection is hereby maintained.

New Objection (s) and/or Rejection (s)

Claim Rejections - 35 USC § 102

Claims 15-17, 59 and 64-71 are rejected under 35 U.S.C. 102(e) as being anticipated by Stamler et al. U.S. Pat. No. 6,255,277 (7/01: filed 5/95: or earlier).

The Stamler et al. patent claims teach (e.g. discloses and claims: see abstract; col. 1-10; examples and patent claims, especially patent claims1-9, 15-34, 40-48 and 54-67) mono- or poly- nitrosated (e.g. SNO) hemoglobin species within the scope of the presently claimed invention for treating (or preventing/inhibiting) plateletet activation and/or thrombus formation which renders such compounds useful for treating cardiovascular disorders including infarction, embolism, thrombophlebitis etc. (e.g. see col. 20, especially lines 38-60).

Double Patenting

Claims 15-17, 59 and 64-71 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-56 (especially claims 1 and 18-23, 29 and 46-51) of copending Application No.10/253,977 (PG PUB: 2003/0072783 A1) alone or in combination with its disclosure (e.g. pages 1-4) for purposes of demonstrating claim interpretation and/or inherency.

Although the conflicting claims are not identical, they are not patentably distinct from each other because Stamler et al. teach that nitric oxide (NO adducts) (e.g upon administration) and S-nitrosothiols (e.g. upon administration or formed in vivo upon NO adduct administration) cause vasodilation and platelet inhibition (e.g. see col 1) which prevents thrombus formation (e.g. see col. 2). Accordingly, the reference teaches that

an administered "nitric oxide adduct" (e.g. a compound or a device comprising a compound: see col. 4) treats damaged vasculature which are susceptible to thrombus formation (e.g see col. 3). The selection of "nitric oxide adducts" of hemoglobin (e.g. (S) nitrosated/nitrated/polynitrosated) is anticipated or in the alternative obvious since hemoglobin is a preferred (e.g. claimed embodiment) "nitric oxide adduct" ie. includes nitrosohemeproteins, with hemoglobin being preferred. Eg. See patent claims 1, 18-24; 30, 36-42,48, and 54-60). See *In re Schaumann*, 572 F.2d 312. 197 USPQ 5 (CCPA 1978). Accordingly, the reference teaches treating (humans/animals) disorders resulting from platelet activation or adherence within the scope of the presently claimed invention (e.g. damaged vasculature) which inherently prevents thrombus formation and platelet activation. E.g. The prior art procedure inherently must prevent thrombus formation and platelet activation because the same protein is applied in the same way in the same amount. *In re Best*, 195 USPQ 430,433 (CCPA 1977); *Ex parte Novitski*, 26 USPQ2d 1389 (B.P.A.I, 1993). Alternatively, the reference teaching of the use of NO adducts and S-nitrosothiols to inhibit platelet inhibit and prevent thrombus formation, where the selection of (S) nitrated/nitrosylated is anticipated or alternatively obvious (e.g. see patent claims), represents an explicit reference teaching anticipation or alternatively rendering obvious the use of these hemoglobins to prevent thrombus formation and platelet activation.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 15-17, 59 and 64-71 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-16 (especially claims 1, 3-6 and 12-16) of copending Application No. 10/413,220 (PG PUB: 2003/0211977A1) alone, or in combination with its disclosure (e.g. pages 1-4; examples) for purposes of interpreting claim scope and/or demonstrating inherency.

Although the conflicting claims are not identical, they are not patentably distinct from each other because Stamler et al. teach that nitric oxide (NO adducts) (e.g upon administration) and S-nitrosothiols (e.g. upon administration or formed in vivo upon NO adduct administration) cause vasodilation and platelet inhibition (e.g. see col 1; examples, particularly Ex. 7) which prevents thrombus formation (e.g. see columns. 2 and 4) for treating/preventing cardiovascular disorders (e.g. "A disorder resulting from platelet activation or adherence"). including cardiac failure and myocardial infarction (e.g. see col. 4, claims 1-4). The selection of hemoglobin (e.g. (S) nitrosated/nitrated/polynitrosated) is anticipated or in the alternative obvious since hemoglobin is preferred (e.g. examples; claimed embodiment) Eg. See patent claims 1-4 and *In re Schaumann*, 572 F.2d 312. 197 USPQ 5 (CCPA 1978) . Accordingly, the reference teaches treating (humans/animals) disorders resulting from platelet activation or adherence within the scope of the presently claimed invention (e.g. cardiovascular disorders or clotting disorders) which inherently prevent thrombus formation and platelet activation. E.g. The prior art procedure inherently must prevent thrombus formation and platelet activation because the same protein is applied in the same way in the same

amount. *In re Best*, 195 USPQ 430,433 (CC PA 1977); *Ex parte Novitski*, 26 USPQ2d 1389 (B.P.A.I, 1993). Alternatively, the reference teaching of the use of NO adducts and S-nitrosothiols to inhibit platelet inhibit and prevent thrombus formation, where the selection of (S) nitrated/nitrosylated hemoglobin is anticipated or alternatively obvious (e.g. see patent claims), represents an explicit reference teaching anticipation or alternatively rendering obvious the use of these hemoglobins to prevent thrombus formation and platelet activation

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 60-63 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-32 (especially claims 1-5) of copending Application No. 09/369,966 (PG PUB: 2002/0037839A1) alone, or in combination with its disclosure (e.g. Fig. 7, pages 9-10; examples) for purposes of interpreting claim scope and/or demonstrating inherency.

The patent application claims teach treating or preventing "a disease or medical disorder which can be ameliorated by delivery of NO" ... by administering to a human or animal nitrosylhemoglobin (e.g see patent claims 1-2).

The patent application claims differ by failing to teach:

a. "a disease or medical disorder which can be ameliorated by delivery of NO" which encompasses "a disorder resulting from platelet activation or adherence" (e.g. myocardial infarction) as in present claims 60-61); or

b. "preventing thrombus formation" (e.g. present claim 62); or

c. "inhibiting platelet activation" (e.g. present claim 63).

However, the patent application defines "a disease or medical disorder which can be ameliorated by delivery of NO" to include "preventing thrombus formation" (e.g. see page 9, right column); "inhibiting platelet activation" (pages 9-10; fig. 7) and disorders resulting from platelet activation or adherence" (e.g. myocardial infarction: see page 10, left column) thus rendering these embodiments obvious to one of ordinary skill in the art. Alternatively, the patent application claimed procedure inherently must prevent thrombus formation and platelet activation because the same protein (e.g. nitrosylhemoglobin) is applied (e.g. administered) in the same way (e.g. to the same host) in the same amount. *In re Best*, 195 USPQ 430,433 (CC PA 1977); *Ex parte Novitski*, 26 USPQ2d 1389 (B.P.A.I, 1993).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 60-63 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-33 (especially claims 1-5) of copending Application No. 10/638,969 (PG PUB: 2004/0132638A1) alone, or in combination with its disclosure (e.g. pages 1-4; examples) for purposes of interpreting claim scope and/or demonstrating inherency.

The patent application claims teach treating or preventing "a disease or medical disorder which can be ameliorated by delivery of NO" ... by administering to a human or animal nitrosylhemoglobin (e.g see patent claims 1-2).

The patent application claims differ by failing to teach:

a. "a disease or medical disorder which can be ameliorated by delivery of NO" which encompasses "a disorder resulting from platelet activation or adherence" (e.g. myocardial infarction) as in present claims 60-61); or

b. "preventing thrombus formation" (e.g. present claim 62); or

c. "inhibiting platelet activation" (e.g. present claim 63).

However, the patent application defines "a disease or medical disorder which can be ameliorated by delivery of NO" to include "preventing thrombus formation" (e.g. see page 9, right column); "inhibiting platelet activation" (pages 9-10; fig. 7) and disorders resulting from platelet activation or adherence" (e.g. myocardial infarction: see page 10, left column) thus rendering these embodiments obvious to one of ordinary skill in the art. Alternatively, the patent application claimed procedure inherently must prevent thrombus formation and platelet activation because the same protein (e.g. nitrosylhemoglobin) is applied (e.g. administered) in the same way (e.g. to the same host) in the same amount. *In re Best*, 195 USPQ 430,433 (CC PA 1977); *Ex parte Novitski*, 26 USPQ2d 1389 (B.P.A.I, 1993).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 17, 59 and 68-71 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-67 (especially claims 1-9, 15-34, 40-48 and 54-67 of US Pat. No. 6,255, 277 B1 (7/01).

Although the conflicting claims are not identical, they are not patentably distinct from each other because the patent claims teach mono- or poly- nitrosated (e.g. SNO) hemoglobin species within the scope of the presently claimed invention for treating (or preventing/inhibiting) plateletet activation and/or thrombus formation.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bennett Celsa whose telephone number is 571-272-0807. The examiner can normally be reached on 8-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-273-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Bennett Celsa

Primary Examiner
Art Unit 1639

BC
July 21, 2004